In This Issue

Cell

The Trade-offs of Cholesterol

PAGE 1213

Cholesterol is an essential component of mammalian membranes. Kwon et al. provide new insight into how cholesterol is transferred into membranes by determining the structure of the N-terminal domain (NTD) of the lysosomal protein Niemann-Pick C1 (NPC1). NPC1 functions with NPC2 to transport lipoprotein-derived cholesterol from lysosomes to other organelles. The authors propose a model by which soluble NPC2 binds cholesterol and hands it off to membrane-bound NPC1, which inserts the cholesterol into lysosomal membranes. These data may help explain Niemann-Pick C disease in which mutations in *NPC1* or *NPC2* disrupt this transfer with lethal consequences.

A Bacterial Etch a Sketch

PAGE 1272

Problem solving with engineered organisms is one of the goals of synthetic biology. Tabor et al. now engineer a community of bacteria capable of cooperatively solving the challenging imaging processing problem of edge detection. The authors combine several genetic circuits that allow the bacteria to detect light, communicate their status to their neighbors, and produce a pigment at the edge between light and dark on a lawn of cells. The system allows "printing" of complex shapes. The authors also develop a quantitatively accurate mathematical model based on the designed gene network. Such models will facilitate engineering of more complex biology behaviors and inform studies of natural regulatory networks.

Sorting out the Signals for Food Avoidance

PAGE 1225

The involvement of neuropeptides in modulating feeding behavior is a developing area of investigation. In this issue, Wu et al. examine a mouse model to understand the source of feeding control rooted in a set of neurons, termed AgRP neurons, that produce the neuropeptides AgRP and NPY and the neurotransmitter GABA. AgRP neuron-ablated mice neither initiate feeding nor consume food delivered directly into their mouths. The authors show that loss of GABA signaling to a nucleus in the brain stem accounts for the anorexic phenotype. Surprisingly, they find that mice can eventually compensate for the loss of AgRP neurons even in adults, which is suggestive of synaptic remodeling.

Copy Number Variation-Based Model of Autism

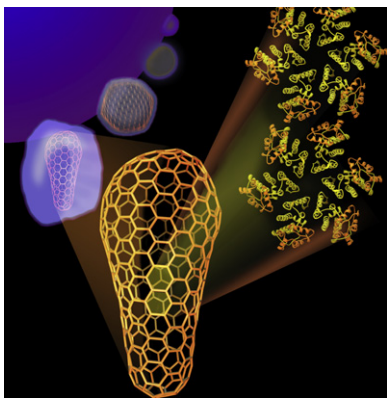
PAGE 1235

The duplication of human chromosome 15q11-13 is the most frequent cytogenetic abnormality associated with autism. In this issue, Nakatani et al. use a chromosome-engineering approach to model this copy number variation in mice. Mice with a paternal duplication of the corresponding region display poor social interaction, behavioral inflexibility, abnormal ultrasonic vocalizations, and correlates of anxiety. Increased expression of a snoRNA within the duplicated region was associated with altered editing of the serotonin 2c receptor mRNA and changes in serotonergic signaling in neurons from the affected mice. This mouse model of autism will serve as a tool for further investigations and for the development of therapeutics.

Nuclear Genome Feels the Hit when Mitochondria Get Punched

PAGE 1247

What is the degree of crosstalk between mitochondrial and nuclear genomes? Veatch et al. report that loss of mitochondrial DNA leads to nuclear genome instability in *Saccharomyces cerevisiae*. This effect is not due to the absence of respiration but instead correlates with a reduction in the mitochondrial membrane potential and a defect in iron-sulfur cluster biogenesis. Given that several proteins necessary for genome integrity require iron-sulfur clusters for their activity, the authors propose that nuclear genome maintenance thus becomes compromised when mitochondrial DNA is lost.

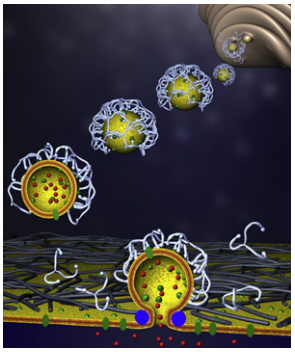


HIV's Deadly Curves

PAGE 1282

HIV's mature capsid is a curved protein shell essential for packaging the viral genome and associated enzymes for delivery into host cells. The capsid is composed of 250 hexamers and 12 pentamers of the CA protein. In this issue, Pornillos et al. report X-ray crystal structures of the CA hexamer. The structures show details of the intersubunit interactions that stabilize the hexamer, including the sites of action of experimental inhibitors of capsid assembly. One part of the hexamer is flexible, and this mobility explains how curvature in the capsid lattice is achieved.

Endocytic Machinery Makes a Dramatic Exit



PAGE 1308

Cell growth and communication with other cells rely on the transport of a variety of molecules across the plasma membrane via vesicle exocytosis. By monitoring individual vesicles carrying biosynthetic cargo from the Golgi to the plasma membrane, Jaiswal et al. observe that exocytosis is Ca^{2+} insensitive and the extent of cargo release can vary from complete to partial to no release. They show that the predominant mode for these post-Golgi vesicles is partial release (due to premature closure of the fusion pore) or no release and that the extent of release can be modulated by clathrin, actin, and dynamin. They thus show that proteins associated with the endocytic machinery can regulate exocytic secretion of biosynthetic cargo.

Retinoic Acid and Estrogen: A Clash of Titans

PAGE 1259

The vitamin A derivative retinoic acid (RA) suppresses the growth of several breast cancer cell lines, whereas the hormone estrogen stimulates growth in these cells. Analyzing the genomic actions of the retinoic acid receptors and estrogen receptor α that mediate the transcriptional effects of RA and estrogen, Hua et al. now find that the two classes of nuclear receptors act as antagonists. The receptors affect the expression of breast cancer-associated genes by competing for binding at the same dispersed genomic regions. This antagonism explains the opposing roles of RA and estrogen in breast cancer growth.

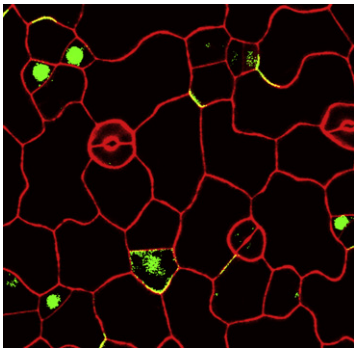
EGFR Latches On

PAGE 1293

Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase that is activated by an asymmetric interaction between its cytoplasmic kinase domains where one domain activates the other. Jura et al. reveal that the juxtamembrane region, which connects the transmembrane helix to the kinase domain, potentiates kinase activity by stabilizing the asymmetric interaction. Part of the juxtamembrane region of the activated kinase domain latches onto the activator kinase, whereas the rest forms an antiparallel helical dimer with the juxtamembrane region from the other EGFR molecule. This helical dimer engages the transmembrane helices and leads to a model for how the activating signal is transmitted across the membrane.

BASL Is a Key Ingredient for Plant Cell Asymmetry

PAGE 1320

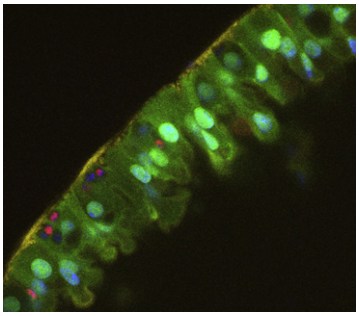


In plants, as in animals, asymmetric divisions are widely used to produce cellular diversity, pattern tissues, and establish stem cell populations. However, constraints imposed by the cell wall, different cell division regulation, and the absence of homologs of animal "asymmetry" genes dictate that plants use fundamentally different molecules and mechanisms to create asymmetries during cell division. Dong et al. have now identified BASL, a new protein that represents a plant-specific solution to this problem. BASL protein accumulates in the nucleus and/or in a polarized peripheral crescent, but in a surprising departure from previously known regulators, BASL is required at the periphery (and not the nucleus) to promote specific cell fates.

Actin' Like a Ratchet in Dorsal Closure

PAGE 1331

During *Drosophila* embryogenesis, a process termed dorsal closure seals an opening in the developing epidermis. Solon et al. examine the physical mechanism of closure and show that individual cells of the tissue that fill the opening produce constitutive, transient force pulses that pull on the surrounding tissue. Dorsal closure then begins when a supracellular actin cable forms around the opening and the transient displacements are translated into net dorsal-ward movement. The actin cable acts like a ratchet, inhibiting ventral-ward relaxation of the epidermis between force pulses. The authors combine these results with simulations to uncover the basis for force generation in this system.



Damaged Gut Epithelium Calls in Replacements, Stat!

PAGE 1343

Intestinal epithelia exist in a state of constant dynamic self-renewal due to the stresses associated with digestion. In this issue, Jiang et al. report that stressed or damaged enterocytes in the *Drosophila* gut produce cytokines that activate Jak/Stat signaling in intestinal stem cells. The stem cells respond by dividing and differentiating, thereby ensuring regeneration of the gut. The study outlines a feedback mechanism that enables stem cells to replace their spent progeny as they are lost and shows how a signaling system most often associated with immunity and inflammation is also used for gut homeostasis.